Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 11, 17, 18 and 19 are pending in the application, with claim 11 being the independent claim. Claims 10 and 16 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claim 11 and 17 are sought to be amended. Support for the amendment to claim 11 can be found, *inter alia*, in Fig. 5 and Example 2 of the specification. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objections to the Claims

The Examiner has objected to claim 10, alleging that the claim appears incomplete in that it fails to set forth with what the portal vein is invaded. Applicants have cancelled claim 10 and believe that this objection is now moot.

The Examiner also objected to claim 11 because the expression "after treatment of the hepatocellular carcinoma has occurred" allegedly does not appear to have antecedent basis. While not acquiescing to the propriety of the Examiner's objection, to expedite prosecution, Applicants have amended the claim to recite that the patient had hepatocellular carcinoma and was subjected to treatment of the hepatocellular carcinoma

in the past. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the objection.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 10 and 17-18 under 35 U.S.C. §102(b) as allegedly anticipated by Furukawa *et al.* and STN Registry file monograph of RN 863-61-6 (cited to explain meaning of menaquinone-4, also known as menatetrenone or vitamin K2). The Examiner has alleged that Furukawa *et al.* teach that administration of menaquinone-4 is effective to decrease plasma levels of des-gamma-carboxy prothrombin in patients suffering from hepatocellular carcinoma (HCC). The Examiner has further stated that menaquinone-4 administered in dosages of 50 mg and 10 mg are taught. The Examiner alleged that while Furukawa *et al.* fail to teach that portal vein invasion was inhibited, because the same substance was administered to the same patients, portal vein invasion was inherently accomplished by the method disclosed by Furakawa *et al.* Applicants respectfully traverse this rejection.

To expedite prosecution, and not in acquiescence of the Examiner's rejection, Applicants have cancelled claim 10 and believe that the rejection is now moot.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 10, 11 and 16-19 under 35 U.S.C. §103(a) as being unpatentable over Furukawa *et al.* and the STN Registry file Monograph of RN 863-61-6 in view of Applicants' acknowledgement in the specification at page 7, lines 1-

5 and Wang *et al.* and further in view of Koike *et al.* Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must show that the cited art suggested to those of ordinary skill that they should make the claimed composition or device, or carry out the claimed method, and that the invention could be attained with a reasonable expectation of success. See *In re Vaeck*, 20 USPQ2d (BNA) 1438, 1442 (Fed. Cir. 1991). Any suggestion and reasonable expectation of success must come from the art of record, not Applicants' disclosure. *Id.*

Applicants note that Koike *et al.* is newly cited against the pending claims. Koike *et al.* sought to elucidate predisposing factors for the development of portal venous invasion (PVI) in patients with HCC. Koike *et al.* reports that des-γ-carboxy prothrombin (DCP), an abnormal prothrombin, correlates with the development of PVI. Koike *et al.* further note that

> prothrombin has been reported to have a potent inhibitory effect on growth of Hep 3B cells, and vitamin K and its analogues inhibit HCC cell growth by suppression of cellular PTPases by sulfhydryl arylation and decrease DCP levels in culture. Therefore, it is possible that vitamin K may effectively suppress the development of PVI in some patients with HCC. A study regarding this hypothesis is in progress currently at our institute.

Koike *et al.* at p. 568 (citations omitted).

With respect to claim 10, the Examiner asserts that because Koike *et al.* teach portal vein invasion (PVI) is developed because of the existence of HCC, and the treatment of HCC was suggested by the cited art, it would have been obvious that any possible complications resulting from HCC, such as PVI, could also be effectively inhibited. To expedite prosecution, and not in acquiescence of the Examiner's rejection,

Applicants have cancelled claim 10 and believe that the rejection, as it applies to claim 10, is now moot.

With respect to claim 11 and claims dependent thereon, the crux of the Examiner's position is that because the cited art suggest that a vitamin K compound is effective treatment for patients suffering from HCC, the cited art would have reasonably suggested the treatment of HCC in any patient, including in a patient who had a previous occurrence of HCC. *See* Office Action, page 5. The Examiner believes that the cited art suggests inhibiting recurrence of HCC because there are two types of patients suffering from HCC, namely one type that is suffering from HCC for the first time and a second type that had HCC in the past and is again suffering from HCC; the Examiner asserted that given such a small genus of patients that would have been presented to one of ordinary skill, the treatment would have been obvious. The Examiner further alleged that arriving at the claimed dosages would have been well within the purview of one of ordinary skill in the art.

The Applicants respectfully disagree with the Examiner's characterization of the cited art. Neither Furukawa *et al.*, Wang *et al.* nor Koike *et al.*, alone or in combination, teach or suggest that menaquinone-4 is an effective *treatment* to inhibit recurrence of HCC.

Furukawa *et al.* are completely silent on the efficacy of menaquinone-4 in treating HCC in patients, let alone inhibiting recurrence of HCC in patients as claimed. Thus, Furukawa *et al.* does not provide any motivation to administer the compound to inhibit recurrence of HCC. Furukawa *et al.* were interested in DCP levels as a marker for vitamin K deficiency and in patients with HCC. DCP is an abnormal prothrombin

that lacks coagulant activity, and accumulates in vitamin K deficient patients possibly due to a vitamin K-dependent gamma glutamyl carboxylase that is required for carboxylating its glutamic acid residues. High DCP levels are also found in HCC patients. Furukawa *et al.* hypothesized that the mechanism leading to high DCP levels in HCC patients differed from that in vitamin K deficient patients and therefore investigated if high DCP levels in HCC patients could be attenuated by vitamin K. Furukawa *et al.* observed that administration of menaquinone-4 reduced levels of DCP in both HCC and vitamin K deficient patients to similar degrees. Importantly, while Furukawa *et al.* administered menaquinone-4 to patients with HCC to measure DCP levels, Furukawa *et al.* make no connection between the lower DCP levels observed in HCC patients treated with menaquinone-4 and its efficacy and/or possible use as a therapy for treating HCC or inhibiting recurrence of HCC in patients. Furukawa *et al.* do not even hint that menaquinone-4 can be used as a therapy for HCC or to inhibit recurrence. Furukawa *et al.* suggest, if anything, that HCC should be treated by resection or arterial embolization. *See* Abstract and p. 32-33 of Furukawa *et al.* Hence, there is no suggestion in Furukawa *et al.* that menaquinone-4 be used to inhibit recurrence of HCC in patients.

While Wang *et al.* report that menaquinone has growth inhibitory effects on the HEP 3B cell line under cell culture conditions, Wang *et al.* do not teach that menaquinone would be effective to inhibit recurrence *in patients* as claimed.

However, assuming *arguendo*, that such a suggestion was found in the cited art, Applicants submit that the skilled artisan would not have any reasonable expectation of success in carrying out the claimed methods. It is almost axiomatic in pharmaceutical

research that an agent's *in vitro* properties are often a poor correlate of their properties *in vivo*. In the field of cancer research, where scores of drug candidates that exhibit promising *in vitro* properties fall by the wayside during clinical trials, this proposition cannot be disputed. It is a fallacy for the Examiner to conclude that just because an agent exhibits growth inhibitory properties against a cell line in cell culture, as reported by Wang *et al.*, it would be an effective therapy against cancer in patients. Applicants submit that a person of ordinary skill in the art would have no reasonable expectation of success in administering an agent to inhibit recurrence of HCC based simply on *in vitro* results of a single experiment. The unpredictability in the art of cancer research and therapy demands that much more is needed to establish a reasonable expectation of success, and thus, a *prima facie* case of obviousness. It is the Applicants' disclosure, and not the disclosure of Furukawa *et al.*, Wang *et al.* or Koike *et al.*, alone or in combination, which establishes that menatetrenone is effective to inhibit recurrence of HCC in patients. Applicants respectfully remind the Examiner that any reasonable expectation of success must come from the cited art of record and not the Applicants' disclosure, otherwise, the Examiner would be engaging in impermissible hindsight.

Accordingly, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness and respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the

Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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